SPARED COGNITIVE PROCESSING OF VISUAL ODDBALLS DESPITE DELAYED VISUAL EVOKED POTENTIALS IN PATIENT WITH PARTIAL RECOVERY OF VISION AFTER 53 YEARS OF BLINDNESS

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ABSTRACT

We examined the visual and cognitive functions of a 72-year-old subject, KP, who recovered his sight after 53 years of visual deprivation. We used visual evoked potentials (VEPs) to pattern-reversal and motion-onset stimuli and cognitive responses (ERPs) during the oddball paradigm to assess the effect of long-term deprivation on a mature visual system. KP lost his sight at the age of 17 years, and light projection onto his right retina was restored at 71 years by a corneal implant. Nine months after sight recovery we recorded reproducible responses to all examined stimuli. The response to pattern reversal contained two P100-like peaks with the later peak being dominant and significantly delayed (260 ms) when compared to the P100s of two control subjects, to whom the stimuli were adjusted in size and contrast to mimic KP's vision. KP's motion-onset VEPs to full-field and peripheral stimuli had a characteristic shape with a well-defined N2 peak; however, both peaks were significantly delayed (262 and 272 ms) compared to control responses. Unlike the P100 and N2 peaks, which represent sensory detection, the P3b/P300 component of the ERP to a target event in the oddball paradigm was not further delayed. In spite of degraded vision and sensory deprivation lasting 53 years, KP displayed reproducible responses to all reported stimuli. Long-term visual deprivation and retinal detachment degraded KP's visual sensory processing, assessed by pattern-reversal and motion-onset VEPs, whereas the cognitive processing of appropriate visual stimuli was not compromised.

KEYWORDS:

Visual deprivation, recovery from blindness, motion-onset VEPs, pattern-reversal VEPs, oddball ERPs, P3b.

INTRODUCTION

Cortical structures involved in the analysis and interpretation of visual information are plastic, and their long-term deprivation can lead to a change in or limitation of visual functions. From the sparse literature, it is known that the restoration of optical projection to the retina after long-term light deprivation is not associated with full recovery of active vision (Valvo, 1972; Carlson and Hyvarinen, 1983; Carlson, Hyvarinen, and Raninen, 1986; Sacks, 1995).

Here we report electrophysiological examination of a 72-year-old subject, hereafter referred to as KP, whose sight was recovered after 53 years of visual deprivation. Measuring evoked/induced brain activity enabled us to assess his cortical functions and to investigate the changes in a fully-matured visual system due to deprivation of normal visual experience.

Examination of such subjects is interesting from the medical point of view, as the development of implantable visual prosthetics is in progress (Ahuja et al., 2011) and the limitations of cortical plasticity are an important issue. In a literature search, we found only one relevant report of pattern-reversal VEPs following vision restoration. Subject MM lost his vision at 3 years and light projection was restored to his right eye after 40 years by corneal replacement (Fine et al., 2003) (supplementary material of the article).

Our aim was to compare KP´s sensory vs. cognitive processing. On the level of sensory detection we assessed VEPs in response to (i) - reversal of a checkerboard pattern to evaluate P100 peaks originating from primary visual areas (V1)(Di Russo et al., 2005; Barnikol et al., 2006) and (ii) - motion-onset of low-contrast structures activating magnocellular input of the dorsal stream (Kuba and Kubova, 1992; Heinrich, 2007) to evaluate the dominant N2 peak originating in extrastriate areas (V3A, V5) (Schellart et al., 2004). On the level of cognitive processing we measured P3b waves recorded in response to visual target stimuli during the oddball paradigm (Duncan et al., 2009). This paper discusses KP's electrophysiological results in detail and compares his sensory and cognitive responses to reactions of two controls examined with stimuli adjusted to match KP's impaired vision.

METHODS

Subjects

KP lost his sight at the age of 17 years due to burning of his cornea caused by an explosion of molten metal in a factory where he worked. The burn left only a sparse sense of light with no form or shape perception.

Full projection of light onto KP's right retina was restored, after a series of unsuccessful corneal implantations, at the age of 71 years (September 2009) by implantation of a Boston KPRO type I keratoprosthesis. The cornea was attached to his eyelid, meaning saccades were limited in either direction. The cornea was opaque and vascularized.

A few weeks after the surgery, his visual acuity was 0.33. We had the opportunity to examine KP 9 months later (June 2010), when his vision had significantly deteriorated. Eleven months after surgery (August 2010), his eye surgeon diagnosed retinal detachment, and KP's vision rapidly

returned to the pre-treatment level. In spite of the short period of regained vision, KP considered this time as "the best gift", allowing him, for example, to see his wife for the first time.

On the day of the examination conducted KP's right eye visual acuity was 0.04 and its contrast sensitivity was 33.8 %; the left eye was without shape/contrast discrimination. Visual acuity and contrast sensitivity were measured before electrophysiological acquisition from the distance used for stimulus presentation (0.6 m) on computer monitor by the Freiburg Visual Acuity Test (4 choices, 24 trials, screen resolution 1600 × 1200 pixels, luminance contrast 96%) (Bach, 2007). Michelson contrast sensitivity was determined using a Landolt's circle of 180 arc min.

KP's responses were compared to the responses of two healthy age-matched controls (C1 and C2) that we recruited by advertisement in a local newspaper. The right eye was examined in all subjects. The visual acuity for C1 was 0.38 and for C2 was 0.74 all examined without correction glasses correspond to natural presbyopia. The contrast sensitivity was 0.9 % for C1 and 2.36 % for C2. Both controls' latencies of assessed VEPs/ERPs components were shorter than 95 percentile of age related subgroup of healthy subjects (n = 35, age 55–85, median 71 years) (Kuba et al. 2012).

We obtained informed consent from KP and both controls after the test procedure was explained. The examination was part of a study approved by the Ethical Committee of the Faculty of Medicine in Hradec Králové, and experiments were conducted in accordance with the Declaration of Helsinki (2004).

Procedure

Examination was performed in a darkened, sound-attenuated, electromagnetically shielded room with a background luminance of 0.1 cd/m^2. During the experiment, the subjects were sitting in a comfortable dental chair with a neck support to reduce muscle artifacts. Correct fixation was monitored via a near-infrared CCD camera.

All stimuli including visual acuity and contrast sensitivity measurement were presented on a 21" computer monitor (Vision Master Pro 510, Iiyama, Japan) subtending 37 × 28 deg of the visual field from observing distance of 0.6 m.

VEP/ERP were recorded from 6 unipolar derivations (O_L, O_Z, O_R, P_Z, C_Z, F_Z) with a right earlobe reference. The minimum set of recording derivations was chosen on the basis of a previous topographical study concerning the scalp distribution of motion-onset VEPs (Kremlacek and Kuba, 1999). The ground electrode was connected to the reference. All electrode impedances were kept below 5 kΩ. After amplification in the frequency band of 0.3–100 Hz (PSYLAB, System 5, Contact Precision Instruments, USA), the signal was stored for offline processing on a personal computer. The recording was synchronized with a backward trace of the monitor's electron beam just before the first video frame of an appropriate stimulus change.

Forty time periods were recorded, and those time periods with amplitudes exceeding 70 μV were rejected (suspected artifacts). The rest of the responses were smoothed by a second-order polynomial Savitzky-Golay filter (across 47 samples).

Pattern-Reversal

Over 20 seconds, forty reversals of a high contrast black and white checkerboard pattern were used to evoke pattern-reversal VEPs. Check size was changed during examination from 40 to 240 arc min, contrast was kept 96 %. Controls were examined using parameters evoking a stable response in KP, i.e., a contrast of 96 % and a check size 160 arc min. Then, to simulate KP's low vision, check size was decreased to *160 arc min* (KP's VA/ controls VA)*, that was 16 arc min for C1 and 9 arc min for C2. The contrast was decreased to two levels: a) the same absolute amount of contrast above controls' contrast threshold (CS) as KP had *(96 % - KP's CS)*, i.e., 60 % for both C1 and C2, or b) a proportion above their contrast threshold *((96 % / KP's CS)* controls CS)*, i.e., 3 % for C1 and 7 % for C2.

The pattern-reversal was presented using Visual Stimulus Generator 2/5 (CRS ltd., UK) at a vertical refresh frequency of 105 Hz. The mean luminance of 17 cd/m^2 was kept constant. 440 ms of post-stimulus EEG sampled at 500 Hz were averaged for VEPs. Subjects were instructed to keep their gaze on the fixation point during recording, which took about 30 s for one VEP.

Motion-Onset

To elicit motion-onset VEPs, we used a radial circular pattern corrected for equal visibility in the whole stimulus field by a magnification factor [CMF = 1/(0.1 × eccentricity [deg] + 1)] used for motion stimuli in our lab (Kremlacek et al., 2004). The local motion velocity increased (5–25 deg/s) while spatial frequency decreased (1–0.2 c/deg) toward the periphery (the temporal frequency of 5.1 c/s was kept constant over the whole stimulus field).

The structure moved for 200 ms and then it was stationary for 1 s. To avoid direction-specific adaptation that would result in a motion after-effect, we changed the motion direction randomly (centrifugal or centripetal).

Two variants of motion stimulation were used: full field and peripheral. During the full field variant, the stimulus occupied the whole monitor area, while for the peripheral variant, the central 20 deg were masked by a grey circle of average luminance with a fixation point in its center.

The Visual Stimulus Generator 2/5 presented motion-onset stimuli at a vertical refresh frequency of 105 Hz and the constant mean luminance of 17 cd/m^2. EEG post-stimulus periods of 440 ms duration was sampled at 500 Hz. Subjects' task was to keep their gaze on the fixation point during recording, which took about 60 s for one VEP. For KP, we had to increase the Michelson contrast to 96 %. Controls were examined using a contrast value of 96 %, 10 % and proportionally above their contrast threshold *((96 % / KP's CS)* controls CS)*, i.e., 3 % for C1 and 7 % for C2.

Oddball

The cognitive processing of visual information was tested in the oddball paradigm. The stimulus consisted of a black outline of a square (the frequent stimulus) and a circle (the rare stimulus) appearing with probability 0.12. ISI was randomized between 1-1.5 s. The object was displayed on a white background, and it subtended 14 deg.

The stimuli were presented using Psychtoolbox 3 (Brainard, 1997) at a vertical refresh frequency of 75 Hz. EEG post-stimulus periods of 1000 ms duration was sampled at 250 Hz,

KP and controls were instructed to press a handheld button as soon as possible whenever the rare stimulus appeared. Before the examination a training phase took place during which KP named each stimulus and pressed the button several times to be confident with the task. Only then we proceed to the recording.

RESULTS

Subject KP

When KP arrived (June 2010) accompanied by his son, he was able to slowly read with an electronic magnifier, but his ability to navigate in an unknown place was limited, so his son's help was necessary to orient himself in the lab.

We started the electrophysiological examination with pattern reversal of a checkerboard of 40 arc min checks, but no readable response was detected. A readable response was evoked by reversal of 160 arc min checks. The pattern-reversal VEP had an atypical shape so we repeated the stimulation four times. The pattern-reversal VEPs from O_Z are plotted on Fig. 1. The shape of the response consisted of two positive peaks (150 and 260 ms), with the later peak dominant and more stable. KP's response to the reversal of 240 arc min checks was again barely recognizable.

The examination of motion-onset VEPs with low contrast stimuli did not have reproducible results. We increased the Michelson contrast to 96% and obtained reliable motion-onset VEPs after full field as well as peripheral stimulation. KP's motion-onset visual-evoked potentials to both full field and peripheral stimuli had a characteristic shape with a well-defined N2 peak. However, the peak was significantly delayed to 262 and 272 ms compared the controls' responses (see Fig. 1).

KP's ability to process motion was verified by a subjective report of an illusory opposite motion after adapting to a moving stimulus, the motion after-effect. The adapting stimulus was radial motion randomly expanding/contracting for 30 sec with the same spatial parameters as the stimulus used for motion onset. This procedure was 3 times repeated. In all cases, when the pattern stopped KP correctly reported that rings were enlarging/decreasing in opposite to adapting motion. He reported to perceive the illusory motion for about 2 seconds.

Before beginning of cognitive ERP recording, KP learned to recognize target (circle) and non-target (square) objects (see Methods). He solved the odd-ball task without difficulties and his P3b had a peak implicit time of 596 ms. KP had 100 % accuracy in responding to targets and no false positive reactions to the frequent stimuli. The shape of the response corresponded to waveforms recorded from healthy controls, with an easily recognizable difference between target and non-target responses (see Fig. 1).

Controls

The controls' pattern-reversal VEPs had a single positive peak dominating the response with a shorter latency than the earlier, less stable peak of KP. Manipulation of the contrast and the size of the checkerboard pattern prolonged the implicit time of the positive peak but did not produce a second peak (see Fig. 1).

The controls' responses to moving stimuli with parameters effective for KP had considerably shorter latencies to the dominant negative peak, in many cases by more than 100 ms. After reduction of the luminance contrast, their implicit time increased by a maximum of 56 ms.

Both controls had a shorter implicit time of the P3b peak (416, 528 ms) compared to KP's (596 ms).

The difference between the slower of the controls' P3b peaks and KP's corresponding peak (68 ms) was comparable to the difference between the slowest negative dominant peak of the controls' motion-onset VEPs and KP's corresponding peak (56 ms). Because the response to target stimuli had a complex shape with two positive peaks in KP's and controls' responses (see Fig. 1), we can also compare the intervals between peaks. The interpeak difference was shorter for KP than for C2. That was not true for the median reaction time because KP responded 300 ms after C2, the slower of the controls.

Despite keen and friendly cooperation, KP only slowly inspected the monitor to find the fixation point or the Landolt's circles during the visual acuity and contrast sensitivity examinations. More extensive testing of KP was limited by his degraded vision.

DISCUSSION

Subjects whose vision was returned after long-term sensory deprivation have a preserved ability to solve simple visual tasks like discrimination of shapes, colors, motion and objects represented in a canonical form, but their processing of more complex visual scenes or faces is impaired (Ostrovsky, Andalman, and Sinha, 2006; Ostrovsky et al., 2009).

Although KP recognized correctly the checkerboard or moving circles, pattern-reversal or motion-onset stimuli evoked severely delayed responses. In the pattern reversal test, the shape of the response also changed. Because of KP's impaired vision, there is a possibility that these deficits are produced by a degraded signal from his retina. However, in controls even a large decrease in the size and contrast of the stimuli did not produce a deficit comparable to KP's. Further support for the dominant effect of prolonged visual deprivation to observed prolongation of KP's sensory responses comes from study of Folk et al. (1984). In their study authors found maximal prolongation of 30 ms of P100 peaks recorded from eyes with retinal detachment due to central serous retinopathy. However, KP's peak mimicking P100 was delayed by at least 98 ms and at the most 160 ms behind controls; for motion-onset the KP's N2 peak lagged by 58 ms or up to 112 ms behind controls (see Fig. 1). This suggests that KP's electrophysiological correlates of the low level of vision (i.e., high contrast change and abrupt motion-onset) are impaired mainly due to long-term deprivation.

The state of active vision depends on factors like the length of deprivation or the age at which sight loss occurred, making reports of subjects with restored vision difficult to compare. For example, early blind subject SB who regained his vision at 52 reported that he could not see a motion aftereffect (Gregory and Wallace, 1963). The opposite was found in the thoroughly studied subject MM. Several papers claim that his motion processing was not affected by 40 years of lasting visual deprivation. Fine et al. (2003) showed that MM and controls had a similar area of BOLD signal increase during activation of MT+/V5, and Levin et al. (2010) demonstrated normal connectivity of his callosal-MT+/V5 area.

Here we report prolonged electrophysiological response to motion-onset corresponding to an impairment of the motion system processing caused by 53 years of visual deprivation in a mature visual system. Also MM displayed BOLD activation in the motion sensitive areas less than half of the BOLD increase in controls (see Fig. 1b in (Fine et al., 2003)), which could be a correlate of the latency prolongation that we observed in the dorsal stream of KP. Interestingly, MM displayed spared motion direction discrimination, object from motion detection or biological motion identification. Behaviorally KP also seemed to be able to correctly detect motion and to see the motion aftereffect during our experiment. This apparent dissociation might origin in different sensitivities of electrophysiological and behavioral tests (Herbst et al., 1997).

Unlike the VEPs, which represent an early correlate of sensory detection, the cognitive responses to target in the oddball paradigm did not show further prolongation. This observation is consistent with the neuropsychological view of P3b as a modality independent component related to attentional/memory update and controlled by top-down networks (Polich, 2007).

Unfortunately, we did not get the opportunity re-examine KP and further assess plasticity in an adult subject with regained vision because his vision was lost three months after our examination because of retinal detachment.

CONCLUSIONS

The visual evoked potentials (VEPs) examination provided evidence of preserved projection of visual information to primary visual area and the extrastriate areas of the dorsal stream even after 53 years of visual deprivation; nevertheless, KP's VEP peaks were severely delayed. The response prolongation did not increase systematically with assessed peak implicit time, and the interval between sensory components and oddball target component P3b was comparable to healthy controls.

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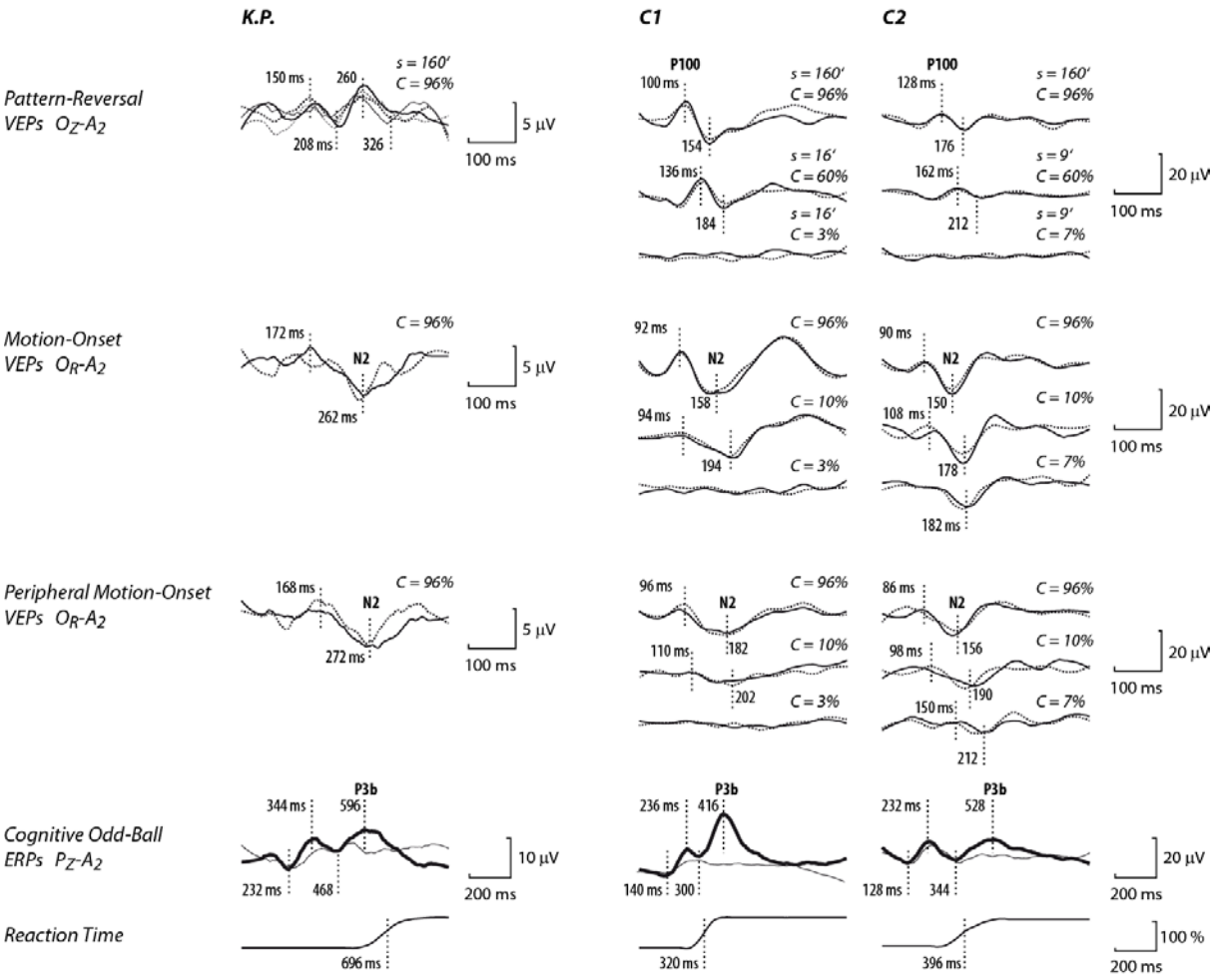

FIG. 1

VEPs/ERPs comparison between KP (left column) and two healthy controls, C1 and C2 (right columns). The first row shows VEPs elicited by reversal of a checkerboard pattern with check size 160' and luminance contrast 96%. The VEPs were recorded four times for KP and twice for controls. To adjust checkerboard visibility for controls to a similar level as KP, we also recorded pattern-reversal VEPs with reduced check size and contrast – see Methods. Motion-onset VEPs are plotted for the full field stimuli and for peripheral stimuli outside the central 20° - labeled peripheral motion-onset VEPs. The lower part of the figure depicts ERPs recorded in the oddball paradigm. The thick line is the response to a rare target stimulus, the thin line to a frequent non-target stimulus. Reaction time evaluated in response to the target stimulus is shown in the bottom row. The curve represents the cumulative distribution function of the button pressing and the median reaction time is indicated.

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